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Liquid Subcutaneous Levodopa-Carbidopa ND0612 Effects on Motor Symptoms in Individuals with Parkinson's Disease: A Systematic Review and Meta-Analysis

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Abstract

Objective: In the manuscript titled "Liquid subcutaneous Levodopa-Carbidopa ND0612 effects on motor symptoms in individuals with Parkinson's Disease: A systematic review and meta-analysis", the objective was to conduct a systematic review with meta-analysis to investigate the effects ND0612 24-hour dosing regimen has on motor symptoms in individuals with Parkinson's Disease (PD). **Introduction:** ND0612 is a novel minimally invasive continuous subcutaneous delivery system of liquid Levodopa-Carbidopa being investigated for the treatment of PD in individuals experiencing motor symptoms. **Methods:** A systematic literature search was conducted in PubMed, Cochrane, and EBSCO databases to identify randomized controlled trials investigating the effects of ND0612 on motor symptoms in individuals with PD. Outcomes included the Unified Parkinson's Disease Rating Scale (UPDRS) Part II and Part III scores. Methodological quality was assessed using the Cochrane Grading of Recommendations Assessment, Development, and Evaluation approach. Meta-analysis was performed using a random effects model with the DerSimonian and Laird method to estimate the effects of the ND0612 24-hour dosing regimen on UPDRS Part II and Part III scores. **Results:** Three studies were included in our review. There were statistically significant reductions in UPDRS Part II scores (mean difference (MD) −3.299; 95% confidence interval (CI) −3.438, −3.159) and in UPDRS Part III scores (MD −12.695; 95% CI −24.428, −0.962) in the ND0612 24-hour dosing regimen. Results were based on very low certainty of evidence. **Conclusion:** Based on very low certainty evidence, the ND0612 24-hour dosing regimen is effective at improving motor symptoms in individuals with PD. Our findings suggest that ND0612 is more effective at improving UPDRS Part II and Part III scores

in individuals with PD than other pharmacological and non-pharmacological treatments, warranting further study.

Keywords

Parkinson's Disease, ND0612, Levodopa-Carbidopa, Motor Symptoms, Motor Complications, UPDRS

1. Introduction

Parkinson's Disease (PD) is a chronic neurodegenerative disease defined by the death of dopaminergic neurons and the development of intraneuronal inclusions (Lewis bodies) in the substantia nigra pars compacta (SNpc) region of the brain [1] [2]. These processes result in dopamine deficiency in the basal ganglia. Dopamine operates in balance with other neurotransmitters to coordinate muscle function [3]. The basal ganglia regulate body function, including muscle movements [4]. Therefore, dopamine deficiency in the basal ganglia is associated with adverse Parkinsonian motor symptoms, including bradykinesia, rigidity, and resting tremor [5]. These Parkinsonian motor symptoms result in dyskinesias, increased risk of falls, and decreased quality of life in individuals with PD [6].

Levodopa is the gold standard medication for managing Parkinsonian motor symptoms. Levodopa temporarily replaces dopamine in the basal ganglia to improve motor symptoms in individuals with PD [7]. Levodopa is metabolized by L-amino acid decarboxylase (AADC), monoamine oxidase (MAO), and catechol-O-methyltransferase (COMT). Because of the role AADC plays in the metabolism of Levodopa, an AADC inhibitor (Carbidopa) is typically co-administered with Levodopa to increase the medication's bioavailability [8].

Oral Levodopa has a short half-life and is associated with increased peaks and valleys in the medication concentration in the blood. The short half-life of oral forms of Levodopa is believed to be an offender in the pathogenesis of motor complications [9]. Levodopa temporarily replaces dopamine, but because the medication needs to be taken several times a day, dopamine levels rise and fall. These fluctuations lead to unstable levels of dopamine in the brain, causing motor symptoms [9].

Over time, oral Levodopa treatment is associated with the development of extraneous motor symptoms, such as motor fluctuations and dyskinesia [10] [11]. One-third of individuals treated with oral Levodopa develop dyskinesias after only two years of exposure [12]. The motor symptoms caused by long-term oral Levodopa treatment can sabotage the initial therapeutic benefit [10]. These motor symptoms result from discontinuous and irregular delivery of Levodopa to the brain [9]. Therefore, it is important to consider other routes and types of medication delivery.

ND0612 (NeuroDerm, Israel) is a novel minimally invasive continuous subcutaneous delivery system of liquid Levodopa-Carbidopa for the treatment

of PD in individuals experiencing motor symptoms. ND0612 is a Levodopa-Carbidopa liquid formulation created for subcutaneous delivery and was designed to combat the adverse complications of oral Levodopa [13]. This form of Levodopa-Carbidopa is particularly beneficial for individuals who experience motor complications that cannot be adequately controlled by the oral form of Levodopa.

ND0612 improves the delivery of Levodopa to achieve more consistent levels of medication concentration in the blood [13]. ND0612 is administered through a pump, 24 hours a day (in the 24-hour dosing regimen), resulting in continuous and stable medication delivery, without fluctuations [7]. In animals with PD, administration of dopamine agonists with short half-lives (*i.e.*, oral Levodopa) is associated with dyskinesia [14] [15] [16], whereas administration of long-acting agonists (*i.e.*, ND0612) is not associated with dyskinesia [17] [18]. The same disparities have been shown in studies comparing pulsatile versus continuous delivery of the same dopaminergic agent [19] [20].

Despite the preliminary evidence of improved long-term motor symptoms with the use of ND0612 24-hour dosing regimen compared to the traditional management with oral Levodopa medication, a systematic review with meta-analysis has not been performed on available evidence to quantify its efficacy when compared with standard of care (SoC) oral Levodopa. Our objective was to conduct a systematic review with meta-analysis to investigate the effects the ND0612 24-hour dosing regimen has on motor symptoms in individuals with PD.

2. Materials and Methods

2.1. Source Data and Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [21]. The review protocol was registered on PROSPERO: ID CRD42023474878 and vetted by a professional research librarian. An extensive literature search on liquid subcutaneous Levodopa-Carbidopa ND0612 was performed using PubMed, Cochrane, and EBSCO electronic databases and manual searches. They were searched from inception to 3rd November 2023. Searches were restricted to articles in the English language and randomized controlled trials (RCTs). Appendix 1 provides a detailed list of search terms utilized.

2.2. Outcome Measures

The Unified Parkinson's Disease Rating Scale (UPDRS) is a frequently used outcome measure to quantify the severity and progression of PD. It includes four sections that assess: 1) mentation, behavior, and mood (UPDRS I), 2) activities of daily living (UPDRS II), 3) motor symptoms (UPDRS III), and 4) complications of therapy in patients with PD (UPDRS IV). Clinicians and researchers use the sectional and total scores to assess the status of PD symptoms and

monitor the disease progress [22]. The UPDRS Part II and Part III scores were used to assess motor symptoms in our review. Estimates of minimal, moderate, and large clinically important differences (CID) for the UPDRS have been determined. On the UPDRS motor score, a minimal CID is 2.3 to 2.7 points, a moderate CID is 4.5 to 6.7 points, and a large CID is 10.7 to 10.8 points, whereas, on the UPDRS total score, a minimal CID is 4.1 to 4.5, a moderate CID is 8.5 to 10.3 points, and a large CID is 10.7 to 10.8 points [23].

2.3. Inclusion and Exclusion Criteria

Studies were included with the following criteria: female and male individuals over the age of 30 with a clinical diagnosis of PD consistent with the UK Brain Bank criteria [24] who have a Hoehn and Yahr (H&Y) Stage 3 or less during the ON state or less than 5 during the OFF state, who take optimized SoC oral Levodopa doses more than once a day, and who's optimized SoC oral Levodopa doses have been maintained stable for at least two weeks. The intervention studied was subcutaneous liquid Levodopa-Carbidopa ND0612 24-hour dosing regimen and the outcomes assessed are UPDRS Part II and Part III scores. The study design search was limited to RCTs published in the English language (Table 1).

Studies were excluded with the following criteria: individuals with previous neurosurgical intervention for PD, a mini-mental state examination score of 26 or less, a clinically significant and unstable medical, surgical, or psychiatric illness, or a history of melanoma/skin disorders. Studies were excluded if other interventions, beyond ND0612 medication, were provided or individuals did not take optimized SoC oral Levodopa medication. Finally, studies were excluded if the outcomes assessed were not UPDRS Part II or Part III scores, or if the study

Table 1. PICOS criteria for inclusion and exclusion criteria of studies.

Parameter	Inclusion criteria	Exclusion criteria
Population	Female and male patients over the age of 30 with a clinical diagnosis of PD consistent with the UK Brain Bank criteria who have a Hoehn and Yahr Stage 3 or less during ON state or less than 5 during OFF state, who take optimized Levodopa doses more than once a day, and whose optimized Levodopa doses have been maintained stable for at least two weeks	Patients with previous neurosurgical intervention for PD, patients with a mini-mental state examination score of 26 or less, patients with a clinically significant and unstable medical, surgical, or psychiatric illness, or patients with a history of melanoma or significant skin disorders
Intervention	Subcutaneous liquid Levodopa-Carbidopa ND0612	Other types of Levodopa-Carbidopa medication
Comparator	No comparator	No comparator
Outcome	UPDRS Part II and Part III as efficacy endpoints	UPDRS Part II and Part III not included as efficacy endpoints
Study design	Randomized Controlled Trials published in English	Expert opinions, editorials, case reports, abstracts without full reports, and preprints. Published in any other language than English

design was expert opinion, editorial, case report, abstracts without full results, and preprints.

2.4. Study Selection

Two reviewers (PA, MW) independently screened all titles and abstracts of the identified studies. Full texts were obtained for the studies deemed eligible from the initial screening. Two reviewers (PA, MW) independently reviewed full texts. Any discrepancies were discussed and resolved through discussion with a third reviewer (KL).

2.5. Data Extraction

Data were extracted into a standardized form that included the lead author, publication date, country, study design, intervention type, sample size, age, and results for UPDRS Part II and Part III outcome measures by one independent reviewer (PA). A second reviewer (MW) conducted a reliability check. No discrepancies in data extraction were identified between the reviewers. UPDRS Part II and Part III scores were used to assess the progression of motor symptoms for individuals with PD. If there was missing data, we contacted the authors for additional information.

2.6. Risk of Bias

Methodological quality was examined using the Cochrane Risk of Bias 2 (RoB 2) tool [25]. The RoB 2 is structured into five domains of bias: 1) randomization process, 2) deviations from the intended interventions (effect of assignment and adhering to intervention), 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported result. From the results in each domain, an overall risk of bias was determined. Overall risk of bias was judged as high risk of bias, some concerns, or low risk of bias. Two reviewers (PA, MW) independently conducted the risk of bias analysis. Any discrepancies were discussed and resolved through discussion with a third reviewer (KL).

2.7. Data Analysis

We performed a random effects meta-analysis using the DerSimonian and Laird method to calculate the mean difference (MD) and 95% confidence interval (CI) of the 24-hour dosing regimen of ND0612 on UPDRS Part II and Part III scores in individuals with PD. The MD and 95% CI were estimated when at least two or more studies included the same UPDRS scores. Of note, the Olanow *et al*. [26] 24-hour dosing regimen included 19 individuals who may have rolled over to the Poewe *et al*. [27] 24-hour dosing regimen. To limit the potential for repeated observations of participants in the meta-analyses and remain consistent with Cochrane recommendations, we decreased the sample size to 71 for the Poewe *et al*. [27] study.

We assessed heterogeneity using Q, p, and I^2 values. The I^2 value of 0% - 40%

was interpreted as not important heterogeneity, 30% - 60% as moderate heterogeneity, 50% - 90% as substantial heterogeneity, and 75% - 100% as considerable heterogeneity [28]. The 95% prediction interval was estimated when the meta-analysis included more than two studies. Publication bias was assessed in meta-analyses with at least ten studies [29]. Publication bias was assessed by inspection of the standard error funnel plots, trim-and-fill analysis, Egger's regression test, and Begg and Mezumdar's rank correlation test. If a meta-analysis did not include at least ten studies, the standard error funnel plot was still generated for qualitative review. All statistical analyses were conducted using STATA 18 (StataCorp. Stata statistical software: release 18. College Station, TX: StataCorp LP. 2023).

2.8. Certainty

Two reviewers (PA, MW) independently assessed the certainty of evidence using the GRADE approach for each meta-analysis (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from gradepro.org) [30]. Discrepancies were discussed and resolved through discussion with a third reviewer (KL). Each meta-analysis was classified as very low, low, moderate, or high-quality certainty of evidence.

3. Results

3.1. Study Selection

The electronic search of databases yielded 45 articles. Twelve articles were found to be duplicates, leaving a total of 33 articles. Eighteen articles were excluded after reviewing titles and abstracts. The remaining 15 articles were retrieved and assessed for eligibility. Twelve articles were excluded because they were conference abstracts. Three remaining articles [7] [26] [27] were found eligible and included in the review (**Figure 1**). Two of the included articles [26] [27] were utilized to perform a meta-analysis. The third article [7] could not be included in the meta-analysis due to missing data. The results of the third article are reported as a narrative.

3.2. Characteristics of Selected Studies

As summarized in **Table 2**, 282 participants were assessed in studies across Israel [7] [26] [27], Europe [26] [27], and the United States of America [26] [27]. The Giladi *et al*. study [7] was divided into two phases, the first phase was two weeks and the second phase was one week. The Olanow *et al*. study [26] was four weeks. The Poewe *et al*. study [27] was 12 months at the time of the results, and it was still planned to continue. The Giladi *et al*. study [7] had a four-week safety follow-up period with a focus on local skin safety, but the other two studies [26] [27] do not mention a follow-up period.

There was an overlap of patients between two of the studies: 21 patients from the Olanow *et al*. study [26] rolled over to the Poewe *et al*. study [27]. All patients

Table 2. Summary of the studies on subcutaneous liquid Levodopa/Carbidopa ND0612 retrieved from the literature.

Authors	Number of participants at baseline	Gender allocation	Mean age of participants	Group allocation	Intervention duration
Giladi et al., 2021	30	70% male, 30% female	63.8 ± 7.4	19 receiving SoC + ND0612 (270/63 mg daily)	2 weeks
Olanow et al., 2020	38	68% male, 32% female	63.5 ± 9.2	19 receiving SoC + 24-hour infusion of ND0612 (720/90 mg) and 19 receiving SC + 14-hour infusion of ND0612 (536/68 mg + 150/15 mg morning oral dose)	4 weeks
Poewe et al., 2021	214	66.4% male, 33.6% female	64 ± 8.9	90 receiving SoC + 24-hour infusion of ND0612 (720/90 mg) and 124 receiving SoC + 16-hour infusion of ND0612 (720/90 mg)	12 months

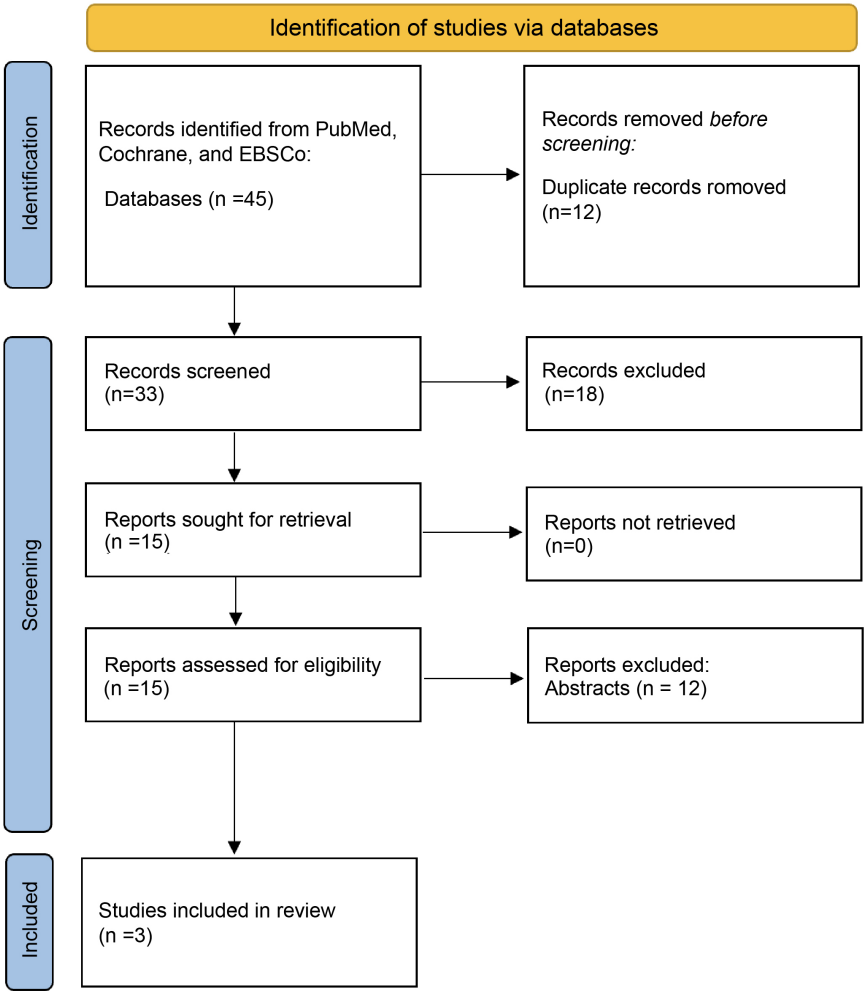

Figure 1. PRISMA flow diagram for searches.

who had previously been assigned to the 24-hour dosing regimen in the prior study [26] continued on this dosing regimen. Patients who had previously been assigned to the 14-hour dosing regimen were switched to the 24-hour dosing regimen. All three studies were RCTs and the intervention was administered

subcutaneously, via a delivery pump system. Different day and night rates were used, with a slower rate at night. In one study [7], the intervention was administered as a 24-hour dosing regimen delivering 270 mg of LD and 63 mg of CD daily. In two studies [26] [27], there were two dosing regimens. In one study [26], there was a 24-hour dosing regimen, delivering 720 mg of LD and 90 mg of CD daily, and a 14-hour dosing regimen delivering 536 mg of LD and 68 mg of CD plus a morning oral dose of 150 mg of LD and 15 mg of CD daily. In one study [27], there was a 24-hour dosing regimen, delivering 720 mg of LD and 90 mg of CD daily, and a 16-hour dosing regimen, delivering 720 mg of LD and 90 mg of CD daily, with different flow rates. One study [7] administered the 24-hour dosing regimen daily for two weeks. One study [26] administered a 24-hour dosing regimen or a 14-hour regimen daily for four weeks. One study [27] administered a 24-hour dosing regimen or a 16-hour dosing regimen daily for one year.

3.3. Characteristics of Participants

The mean age of individuals ranged from 63.5 to 64 years. The H&Y Stage of individuals was 3 or less during the ON state or less than 5 during the OFF state. Baseline characteristics of the individuals in the 24-hour dosing regimen in the Olanow *et al*. study [26] reported that one individual had an H&Y score of 1, 13 individuals had an H&Y score of 2, four individuals had an H&Y score of 2.5, and one individual had an H&Y score of 3. The baseline characteristics of the patients in the 24-hour dosing regimen in the Poewe *et al*. study [27] did not report the H&Y scores. Individuals were taking optimized oral Levodopa doses more than once a day and these doses were maintained stable for at least two weeks. Olanow *et al*. [26] reported 15 adverse events occurred (78.9%), two of which were serious adverse events (10.5%) and two of which led to study drug discontinuation (10.5%). The serious adverse events were an abscess at the infusion site, orthostatic hypotension, and suspected panniculitis. Poewe *et al*. [27] reported 78 adverse events (86.7%), 17 of which were serious adverse events (18.9%) and 17 of which led to study drug discontinuation (18.9%).

3.4. Study Quality

The overall risk of bias was some concern for one included study [7] and high risk for two included studies [26] [27] (**Figure 2**). The main cause of concern in one study [7] was the lack of information regarding randomization and intervention allocation techniques. The main determinants of bias in the other two studies [26] [27] were the lack of participant and caretaker blinding, the inconsistent reports of participants at differing times, and missing data due to participant drop-out.

3.5. Study Outcomes

All included studies assessed outcomes immediately following the intervention. In all three studies, the UPDRS Part II and Part III scores were efficacy endpoints.

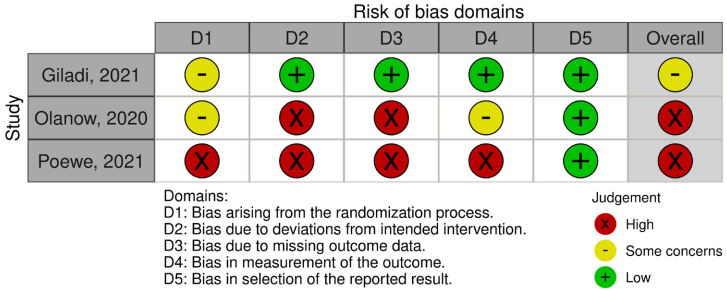

Figure 2. Traffic-light plot of RoB 2.

One study [7] did not separate the UPDRS scores which inhibited the study from being included in the meta-analyses. Giladi *et al.* [7] found that the UPDRS Part I+II+III score with ND0612 showed a positive effect (MD −11.7 +− 14.5) on the non-motor and motor aspects of experiences of daily living and motor examination of individuals with PD. We were unable to perform a comparison between ND0612 and SoC oral Levodopa treatment because there was no data available on the doses of SoC oral Levodopa taken. This was a deviation from the developed protocol.

3.6. UPDRS Part II

The overall effect size of UPDRS Part II scores (n = 88) was statistically significant with an MD of −3.299 [95% CI −3.438, −3.159]. This effect size is a minimal to moderate CID for the UPDRS score [23]. There was a low and no significant degree of heterogeneity identified in the meta-analysis (Q = 0.12, p = 0.73, I^2 = 0.00%) (**Figure 3**). Due to only two studies included in the meta-analysis, the 95% prediction interval was not estimated. Qualitative evidence of potential publication bias was observed in the funnel plot (Appendix 2). A comprehensive assessment of publication bias was not performed due to the limited number of studies included in the meta-analysis.

3.7. UPDRS Part III

The overall effect size of UPDRS Part III scores (n = 88) was statistically significant with an MD of −12.695 [95% CI −24.428, −0.962]. This effect size is a large CID for the UPDRS motor score [23]. There was a large and significant degree of heterogeneity identified in the meta-analysis (Q = 14.77, p = 0.00, I^2 = 93.23%) (**Figure 4**). Due to only two studies included in the meta-analysis, the 95% prediction interval was not estimated. Qualitative evidence of potential publication bias was observed in the funnel plot (Appendix 3). A comprehensive assessment of publication bias was not performed due to the limited number of studies included in the meta-analysis.

3.8. Overall Quality of Evidence

For both the UPDRS Part II and Part III meta-analyses, the risk of bias, indirectness, and imprecision was very serious, and publication bias was strongly

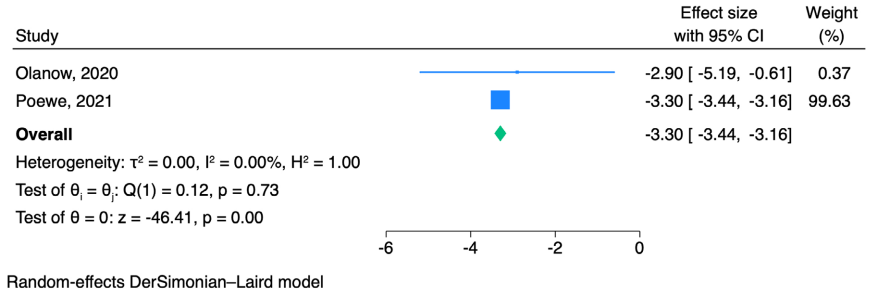

Figure 3. Forestplot UPDRS Part II scores.

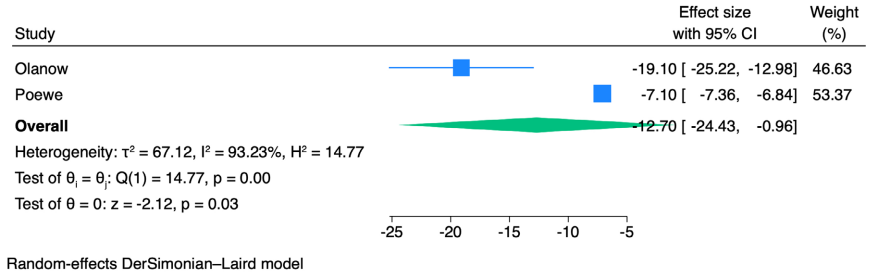

Figure 4. Forestplot UPDRS Part III scores.

suspected, causing the overall certainty of evidence to be very low. Inconsistency was not serious for the UPDRS Part II meta-analysis and very serious for the Part III meta-analysis (Appendix 4 and 5).

4. Discussion

This is the first systematic review to assess the effects of ND0612 liquid subcutaneous Levodopa-Carbidopa 24-hour delivery system on motor symptoms in individuals with PD. Our study revealed there is very low certainty of evidence that significant improvements in UPDRS Part II and Part III scores occur in individuals with PD treated with a continuous ND0612 liquid subcutaneous 24-hour delivery system. Despite the very low certainty, our study provides foundational evidence as to the effects of ND0612 on UPDRS Part II and Part III scores. The main strength of this review was the focus of the research question on UPDRS Part II (motor aspects of activities of daily living) and UPDRS Part III (motor examination) scores.

4.1. Motor Complications

Motor complications (*i.e.* bradykinesia, reduced balance, resting tremor) can significantly impact the quality of life in those with PD [31]. These motor complications increase the risk of adverse events, including falls and injury. To reduce the risk of adverse events, it is important to investigate further medications that can sustain improvement in motor function over time. ND0612 is known to improve motor complications in individuals with PD compared to SoC oral Levodopa [7]. Our findings that ND0612 significantly improves UPDRS Part II

and Part III scores are supported by others [7] who studied ND0612 (MD = −11.7) administered with SoC oral Levodopa compared to placebo (MD = −9.3) administered with SoC oral Levodopa for two weeks. Our study and others [7] suggest that in a short time (two weeks), ND0612 had clinically meaningful improvements in UPDRS scores compared to SoC oral Levodopa.

Of the participants included in our study, approximately 80% experienced an adverse event and up to 19% had a serious adverse event [26] [27]. While concerning, the prevalence of adverse events observed for individuals with PD receiving ND0612 treatments was consistent with others who received Rasagiline treatments (60.5% - 79.5%) [32] [33] and placebo interventions (78.5% - 84%) [32] [33]. The prevalence of adverse events across treatments was not surprising due to the progressive nature of PD that makes individuals with PD more vulnerable to accidental injury, arthralgia, asthenia, back pain, headaches, and infection.

4.2. ND0612 and Rasagiline

Beyond ND0612, Rasagiline has been used to improve UPDRS scores in individuals with PD. Rasagiline is a monoamine oxidase-B (MAO-B) inhibitor, in the oral form that inhibits dopamine metabolism, decreasing Parkinsonian motor symptoms [34]. A study investigating the effects of oral Rasagiline found significant improvements in UPDRS scores (MD −1.8 to 3.6), regardless of the dose of medication (ranging from 1 mg to 4 mg) [35]. A 26-week study found statistically significant improvements in UPDRS scores at dosing regimens of 1 mg (MD = −4.20) and 2 mg (MD = −3.56) of oral Rasagiline [32]. Subsequently, UPDRS scores were significantly improved (MD = −1.82; −2.29) when oral Rasagiline was administered over 52 weeks [33].

Even though UPDRS scores improved with oral Rasagiline, the improvement was smaller than our findings of the effects of ND0612 on UPDRS scores. Future research should investigate the long-term effects of ND0612 versus Rasagiline on UPDRS motor scores in a randomized controlled environment.

4.3. ND0612 Regimens

One reason ND0612 may have a larger effect on UPDRS scores is the continuous delivery that the subcutaneous administration provides. This is demonstrated by the comparison of the 24-hour dosing regimen to the 14-hour dosing regimen. Individuals receiving the 24-hour dosing regimen of ND0612 had decreased UPDRS scores by a greater extent than individuals receiving the 14-hour dosing regimen of ND0612 and a morning oral dose of Levodopa [26]. The 24-hour dosing regimen of ND0612 provides continuous delivery of Levodopa to the brain, decreasing peaks and valleys in the medication concentration in the blood and therefore decreasing motor complications. In the Olanow *et al.* study [26], significant improvements were observed for the UPDRS Part II score (MD = −2.9) and the UPDRS Part III score (MD = −19.1) for the individuals receiving

the 24-hour dosing regimen. Improvements were also observed for the UPDRS Part II score (MD = −1.9) and the UPDRS Part III score (MD = −10.7) for the individuals receiving the 14-hour dosing regimen and a morning dose of oral Levodopa, however, to a smaller extent. Future research should investigate the long-term effects of ND0612 different dosing regimens on UPDRS motor scores in a randomized controlled environment.

4.4. Non-Pharmacological Treatments

Beyond the pharmacological treatments, exercise has been used to improve UPDRS scores for individuals with PD. Yang *et al*. [36] conducted a meta-analysis including 22 studies with a total of 809 individuals. They found that exercise significantly improved UPDRS Part III scores (MD = −5.83) and total UPDRS scores (MD = −7.80) [36]. Although exercise significantly improved the UPDRS motor scores, our study found that ND0612 improved the scores to a larger extent.

In clinical practice, rarely is PD management provided in isolation. To achieve the greatest improvement in UPDRS scores, our findings suggest that structured and supervised exercise should be provided as an adjunct intervention to ND0612. Future research should investigate if UPDRS motor scores can be improved to an even larger extent when individuals receiving ND0612 engage in a structured and supervised exercise program.

Despite the very low certainty of evidence, our findings suggest ND0612 may be more effective at improving motor symptoms than other pharmacological and non-pharmacological treatments. Future research is needed to investigate further ND0612 and the combination of ND0612 with other pharmacological and non-pharmacological treatments.

4.5. Study Limitations

There was a limited number of RCTs on ND0612, a novel medication in the market of PD drugs, compared to SoC oral Levodopa. Only three studies were included in the review. In addition, there was a large and significant degree of heterogeneity in the UPDRS Part III meta-analysis. There were repeated observations in the meta-analyses due to participant rollover. Finally, studies included in our review had a high risk of bias, specifically a lack of randomization in one study. The Olanow *et al*. study [26] and the Poewe *et al*. study [27] were open-label studies, meaning that both the participants and the caregivers knew which regimen of ND0612 the individual was assigned to. The lack of blinding could have biased the outcomes.

5. Conclusion

Based on low certainty of evidence, our study revealed ND0612 significantly improved UPDRS scores. When compared to pharmacological and non-pharmacological treatments for PD, ND0612 had larger effects on UPDRS scores. Future

research should investigate the long-term effects of ND0612 on UPDRS scores in a randomized controlled environment. Future research should not only investigate the effects of ND0612 on UPDRS scores but also compare them to other pharmacological and non-pharmacological treatments. The effects of combined treatments should also be investigated further to understand the clinical implications in individuals with PD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix 1

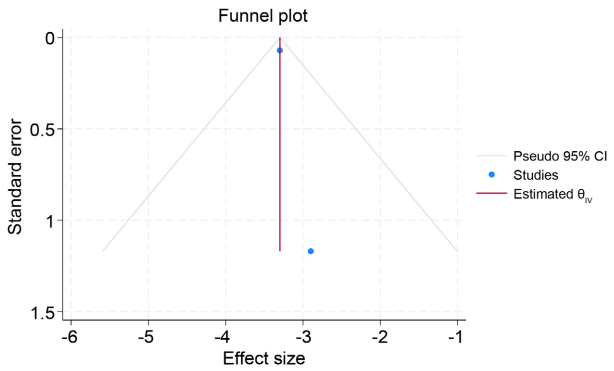
Search terms:

The search terms for the PubMed database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("ND0612" OR "liquid subcutaneous Levodopa-Carbidopa") AND ("motor" OR "mobility" OR "gait" OR "balance" OR "dyskinesia" OR "falls" OR "slowness" OR "rigidity" OR "tremor" OR "ADL" OR "activities of daily living" OR "function" OR "functional mobility" OR "UDPRS"). Filters: Randomized Controlled Trials (RCTs), Humans, English, Exclude preprints.

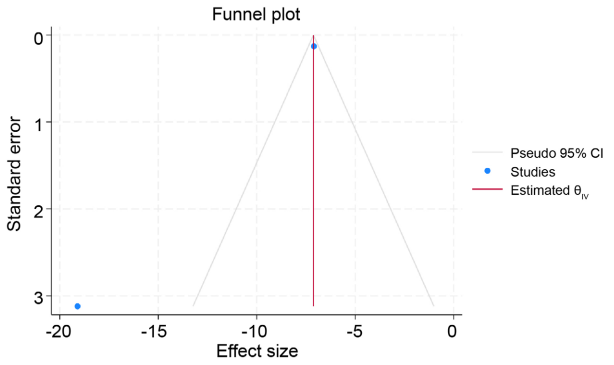
The search terms for the Cochrane database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("ND0612" OR "liquid subcutaneous Levodopa-Carbidopa") AND ("motor" OR "mobility" OR "gait" OR "balance" OR "dyskinesia" OR "falls" OR "slowness" OR "rigidity" OR "tremor" OR "ADL" OR "activities of daily living" OR "function" OR "functional mobility" OR "UDPRS"). Filters: English.

The search terms for the EBSCO database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("ND0612" OR "liquid subcutaneous Levodopa-Carbidopa") AND ("motor" OR "mobility" OR "gait" OR "balance" OR "dyskinesia" OR "falls" OR "slowness" OR "rigidity" OR "tremor" OR "ADL" OR "activities of daily living" OR "function" OR "functional mobility" OR "UDPRS"). Filters: Search mode "find any of my search terms", English.

Appendix 2



Appendix 3



Appendix 4

Question: ND0612 compared to SoC oral Levodopa for patients with Parkinson's Disease.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ND0612	SoC oral Levodopa	Relative (95% CI)	Absolute (95% CI)	
UPDRS Part II score (assessed with: MD)											
3	randomised trials	very serious[a]	not serious	serious[b]	very serious[b]	publication bias strongly suspected[b]			-	0 (0 to 0)	⨁◯◯◯ Very low

CI: confidence interval.

Explanations:

a. Lack of information regarding randomization and intervention allocation techniques;

b. Limited number of studies.

Appendix 5

Question: ND0612 compared to SoC oral Levodopa for patients with Parkinson's Disease.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ND0612	SoC oral Levodopa	Relative (95% CI)	Absolute (95% CI)	
UPDRS Part III score (assessed with: MD)											
3	randomised trials	very serious[a]	very serious[c]	serious[b]	very serious[b]	publication bias strongly suspected[b]			-	**0** (0 to 0)	⨁◯◯◯ Very low

CI: confidence interval.

Explanations:

a. Lack of information regarding randomization and intervention allocation techniques;

b. Limited number of studies;

c. Large and significant degree of heterogeneity.